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Clinical Manifestation of Hereditary Hemochromatosis and Prevalence of Hepatocellular Carcinoma in the Swiss Hemochromatosis Cohort

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Table of Contents

1 List of Tables

2 Summary

Hereditary hemochromatosis (HH) is the most common identified genetic disease in Europe, occurring with a prevalence of roughly one in 200 individuals (1-4). Through the advances in diagnosis and the deeper insight into the genetic background, the clinical manifestation of HH has shifted to a milder picture over the last decades (5-8). However, HH still carries an increased risk of hepatocellular carcinoma (HCC) (9-12).

Our study aims to provide current data on the clinical manifestation of HH among patients with clinically documented iron overload. By presenting a more accurate picture of HH, we support the early diagnosis of the disease to prevent life-threatening complications. We analyzed the prevalence of HCC in our cohort. Additionally, we tried to identify risk factors for HCC with the goal of effective screening measures in mind.

From an established database of HH patients, patient charts were analyzed for the clinical presentation at the time of diagnosis of HH. Information on current health status and liver imaging was gathered to determine the prevalence of HCC. Univariate comparison and multiple logistic regression were used to asses risk factors associated with the development of HCC.

In our cohort, 29% of all patients presented without signs or symptoms of secondary organ damage at the time of diagnosis of HH. The most frequent clinical abnormalities were arthropathy of the metacarpophalangeal joints (MCP joints) and elevated liver enzymes. The overall prevalence of HCC in our cohort was 9%. Factors associated with the development of HCC among patients with high iron overload (serum ferritin >1000µg/l) on univariate analysis were age at diagnosis of HH, body mass index, serum ferritin levels and liver fibrosis. On multiple logistic regression, only age at diagnosis of HH showed a significant association with HCC.

In conclusion, three main findings result from our study: (1) Arthropathy of the MCP joints and elevated liver enzymes are the most frequent and relatively early signs of HH. Their presence should prompt further investigation. (2) HCC is still an important complication of HH. (3) Besides liver cirrhosis and the degree of iron overload, two well established risk factors for the development of HCC (10,13), age at diagnosis of HH seems to be an important risk factor, especially among patients with high iron overload.

3 Introduction

3.1 Background and Context

Hereditary hemochromatosis (HH) is the most common identified hereditary disease in Caucasians, particularly among people of Nordic and Celtic ancestry (1-4,14). It is transmitted in an autosomal recessive pattern (6,15). In populations of northern European origin, the prevalence of homozygosity for the underlying HFE gene mutations is estimated at 0.5%, the prevalence of heterozygosity at 10% (1-4,14).

The diagnosis of HH and the understanding of its genetic background and pathophysiology have changed dramatically over the last decades. The first important step was the discovery of serum ferritin as a marker for total body iron stores (16,17). In the pre-ferritin era, secondary organ damage such as arthropathy, diabetes or hepatopathy was necessary to raise clinical suspicion and diagnosis was later confirmed by liver biopsy (5,6). The availability of serum ferritin has made it possible to diagnose and treat iron overload before clinical manifestation and irreversible organ damage. If treated early, especially before the development of liver cirrhosis or hepatocellular carcinoma (HCC), patients with HH have a normal life expectancy (5,9-12).Therefore, the clinical presentation of HH in daily practice has shifted to a milder manifestation of the disease; patients presenting with the classical triad of bronze complexion, liver cirrhosis and diabetes have become rare (5-8).

The discovery of the underlying gene mutations in 1996 allowed for genetically based population studies and new insight into the variability of the genotype-phenotype correlation, which is significantly wider than initially assumed (2-4,18). The principal genetic defect is a G-to-A missense mutation leading to the substitution of tyrosine for cysteine at position 282 of the HFE protein product (C282Y) (15,19). C282Y homozygosity is found in 85-95% of patients with HH (4,15,19). Another mutation, H63D (substitution of aspartate for histidine at position 63) is identified less frequently (15,19). There has been extensive research on the additional factors necessary to develop the clinical picture of HH (20,21). An important step is the discovery of hepcidin, a key regulating hormone of iron metabolism (22). Patients with HH have abnormally low hepcidin levels despite high iron levels (23,24), leading to uninhibited iron absorption in the gut (23). The resulting iron overload and its organ toxicity is responsible for the clinical picture of HH.

However, despite these major scientific advances, HH still carries an increased risk of liver cirrhosis and HCC (13). Both cirrhosis and HCC contribute largely to the increased mortality due to HH (5,25). Reports of the magnitude of the risk of HCC vary considerably, ranging roughly from a 20- to a 200-fold increase (5,9,11,12,25-30). This variability is partly explained by different study designs, e.g. clinical cohorts in tertiary centers vs. population based studies.

3.2 Scope and Objectives

In the light of this changing picture of hemochromatosis, we aimed to provide current data on the clinical manifestation of HH. By analyzing a large cohort recruited from a tertiary center as well as primary care, we are able to present a more accurate picture of the present-day manifestations of HH than the classical engram of "bronze diabetes". This is especially important since early recognition and treatment of the disease prevent life-threatening complications (5,10,25).

Against the background of the wide variation in the reported risk of HCC (5,9,10,12,25-27,31), we determined the prevalence of HCC in our cohort. We think this is important as HCC is an often fatal complication of HH and the knowledge of its frequency helps in caring for patients affected by HH. We analyzed the risk factors associated with development of HCC, especially among patients with high iron overload, to better identify those patients most at risk.

4 Methods

Approval for this study was obtained from the Ethics Committee of the Canton of Zurich, Switzerland. All patients participating in the study gave written informed consent. We contacted all patients registered in an established database of HH patients, the Swiss Hemochromatosis Cohort. The cohort includes all patients treated at the University Hospital of Zurich as well as patients treated in primary care. The patients treated outside our institution were recruited through the Swiss Hemochromatosis Support Group or at public information events for patients with HH. The patients in the cohort were diagnosed with HH either because of clinical or biochemical abnormalities or through family screening.

All patients with genetically proven HFE-related hemochromatosis (C282Y homozygotes, C282Y/H63D compound heterozygotes or H63D homozygotes) and documented iron overload were considered eligible for the study. For patients diagnosed with HH before the era of genetic testing, genetic analysis was performed during previous studies conducted in the same cohort. Iron overload was defined as elevated serum ferritin (>300 µg/l for men, >200 µg/l for women) and/or elevated transferrin saturation (>50% for men, >45% for women).

In addition to the analysis of pre-existing clinical records, all patients and their treating physicians were contacted to gather current information on their health status and most recent liver imaging.

The following variables had been collected at the time of diagnosis of HH: type of HFE-gene mutation, age, sex, serum ferritin level, transferrin saturation, elevation of transaminases, histological result of liver biopsy, serologic testing for hepatitis B and C and clinical manifestation. The following features were considered clinical manifestations of HH: arthropathy (notably of the metacarpophalangeal joints (MCP joints)), diabetes mellitus, hepatopathy, cardiomyopathy and hypogonadism. The presence of arthropathy was assessed by history and clinical examination. Hepatopathy was defined as either elevated liver enzymes (aspartate and/or alanine transaminase above the upper limit of normal as indicated by the corresponding laboratory) or positive liver histology. Positive liver histology was defined as severe, portal-portal bridging fibrosis or cirrhosis, corresponding to grade 3 and 4 on a scoring system from 0 to 4 (32,33). Cardiomyopathy was specified as either dilated or restrictive cardiomyopathy with documented cardiac iron overload. The diagnosis of hypogonadism was based on clinical characteristics (erectile dysfunction) in combination with laboratory data (i.e. low testosterone levels).

The following variables were recorded during the course of the disease or at the time of the present study: amount of iron removed through phlebotomy until achievement of a serum ferritin level of less than 300 µg/l (assuming that 500 ml of blood removed correspond to 250 mg of iron), body mass index (BMI), date and result of most recent liver imaging studies (ultrasonography, computed tomography scan or magnetic resonance imaging) and AFP (alpha-fetoprotein) measurements, and considerable alcohol consumption. Considerable alcohol consumption was defined as intake of more than 20 g (males) or more than 10 g (females) of ethanol per day.

All patients except one - who refused therapy - received treatment with intensive phlebotomies from the time of diagnosis until depletion of iron stores followed by maintenance phlebotomies where necessary. There was no uniform protocol for surveillance for HCC in our cohort. Implementation of screening measures depended on the treating physician.

HCC was confirmed by biopsy in all patients. Patients without focal hepatic lesions on imaging studies were considered negative for HCC.

Statistical analysis was performed using the IBM SPSS statistics 22 software package (34). Variables were compared using the Student's *t* test, the Mann-Whitney *U* test or the Fisher's exact test (all two-tailed). A p value of <0.05 was considered significant. Multiple logistic regression was used to assess for the independent effects of relevant variables on the outcome. To correct for small sample bias and to deal with the problem of quasi-complete separation, Firth's penalized maximum likelihood estimation (35) was used for the multiple logistic regression analysis performed with *R* (36).

5 Results

51 patients from our database were excluded from the study for various reasons: 12 patients did not wish to participate, 2 never had documented iron overload, 3 did not have HFE-related mutations, 1 patient suffered from concurrent hereditary spherocytosis, and 33 patients could not be contacted.

5.1 Clinical Presentation of Hereditary Hemochromatosis

The main clinical and biochemical characteristics at the time of diagnosis of the remaining 147 patients in our cohort are shown in Table 1.

Table 1. Main Clinical and Biochemical Characteristics at the time of Diagnosis of HH

	All patients (n=147)
Age at diagnosis, years	48±14
Male sex, % (n)	70% (100)
Body mass index, kg/m²	25±4
Mutation: C282Y homozygotes, % (n)	96% (141/147)
C282Y/H63D compound heterozygotes, % (n)	3% (4/147)
H63D homozygotes, % (n)	1% (2/147)
Serum ferritin, µg/l (Q1, Q3)	1448 (727, 2285)
Transferrin saturation, % (Q1. Q3)	89% (79%, 95%)
Iron removed by phlebotomy until depletion of iron stores, g (Q1, Q3)	4.1 (1.6, 9.5)
MCP-arthropathy, % (n)	42% (59/141)
Liver disease % (n)	55% (77/140)
Elevated liver enzymes, % (n)	53% (73/137)
Liver fibrosis on biopsy*, % (n)	51% (36/70)
Diabetes mellitus, %, (n)	8% (11/143)
Cardiomyopathy, % (n)	0.7% (1/143)
Hypogonadism, % (n)	7% (10/142)
Considerable alcohol intake**, % (n)	23% (33/145)

Values are means±1 SD for normally distributed values and medians with first and third quartile for non-normally distributed values

* Liver fibrosis is defined as either cirrhosis or severe, portal-portal bridging fibrosis

** Considerable alcohol intake is defined as consumption of more than 1 standard drink (=10g ethanol) per day for women and more than 2 standard drinks for men

The mean age at diagnosis of HH was 48 years (range 18 to 89 years). 70% of the patients were male. The majority of patients (141/147) were C282Y homozygotes. Serum ferritin levels ranged from 49 to 9180 µg/l with a median of 1448 µg/l. Transferrin saturation was almost uniformly elevated. 29% of patients did not show any organ-specific clinical manifestations. The most frequent clinical manifestations were arthropathy, notably of the MCP-joints, prevalent in 59 of 141 patients, and liver disease, recorded in 77 of 140 patients. Liver disease was mostly manifest in the form of elevated liver enzymes. Only 70 patients in our cohort underwent liver biopsy; 36 of these showed severe fibrosis or cirrhosis. The classical feature of diabetes mellitus was rather infrequent in our cohort with only 8% of patients affected. Hypogonadism was prevalent in 7% of patients. Cardiomyopathy due to iron overload was very rare in our cohort with only one affected patient.

5.2 Prevalence of Hepatocellular Carcinoma and Characteristics of Affected Patients

For the analysis of the prevalence of HCC and its risk factors, 17 patients were excluded because they had never undergone liver imaging, and 13 were excluded because they had deceased and no information about their cause of death was available. The 117 patients included in the analysis were diagnosed between 1971 and 2013, the mean length of retrospective follow-up was 14 years (range 1 to 40 years).

Ten patients were diagnosed with HCC, resulting in an overall prevalence of 9%. We further analyzed the prevalence of HCC among subgroups stratified according to two of the most important risk factors, ferritin and cirrhosis (13,37). Of patients with a serum ferritin level higher than 1000 µg/l at the time of diagnosis of HH, 14% (10/69) developed HCC. When analyzing only patients with a serum ferritin level higher than 2000 µg/l, the resulting prevalence is 21% (7/34). Of those patients with positive liver histology, 33% (9/27) were eventually diagnosed with HCC .

All ten patients suffering from HCC were male and affected by a homozygous C282Y mutation. None of them suffered from concurrent chronic viral hepatitis. They all showed MCP arthropathy and elevated liver enzymes at the time of diagnosis of HH. One patient had a normal liver biopsy, while the other nine suffered from severe fibrosis or cirrhosis. The time span from diagnosis of HH to detection of HCC ranged from zero to 30 years. Four out of nine patients had normal levels of AFP at the time of diagnosis of HCC.

5.3 Risk Factors for Hepatocellular Carcinoma

To determine possible risk factors for HCC, we compared the main clinical and biochemical characteristics at the time of diagnosis of HH between patients with and without HCC. Table 2 shows this juxtaposition with the statistical significance of the differences based on univariate analysis. Patients with HCC were significantly older when diagnosed with HH; the youngest patient later suffering from HCC was 40 years old at the time of diagnosis of HH. Although all patients with HCC were male, sex did not proof to be a significant variable. Serum ferritin levels were significantly higher in HCC patients, ranging from 1329 to 6807 µg/l, as was the amount of iron removed through phlebotomy, ranging from 7 to 18 g. The year of diagnosis did not differ significantly. MCP arthropathy, elevated liver enzymes and positive liver histology all showed a significant difference between the two groups.

Table 2. Comparison of Main Characteristics at the Time of Diagnosis of HH between Patients with and without HCC

	HCC (n=10)	no HCC (n=107)	p-values
Age at diagnosis, years	61±11 (40-80)	47±13 (19-76)	0.003
Male sex, % (n)	100% (10)	69% (74)	0.060
Body mass index, kg/m²	27±3	25±4	0.065
Serum ferritin, µg/l (Q1, Q3)	3704 (2025, 4463)	1338 (691, 2468)	<0.001
Iron removed by phlebotomy until depletion of iron stores, g (Q1, Q3)	8.9 (7.2, 10.1)	3.8 (1.6, 8.9)	0.029
MCP-arthropathy, % (n)	80% (8/10)	44% (44/104)	0.042
Elevated liver enzymes, % (n)	100% (10/10)	53% (53/100)	0.005
Liver fibrosis on biopsy*, % (n)	90% (9/10)	37.5% (18/48)	0.004
Diabetes mellitus, %, (n)	10% (1/10)	7% (7/104)	0.532
Hypogonadism, % (n)	20% (2/10)	6% (6/104)	0.146
Considerable alcohol intake**, % (n)	20% (2/10)	26% (27/105)	1
Year of diagnosis (Q1, Q3)	2001 (1990, 2003)	1999 (1996, 2007)	0.476

Values are means±1 SD for normally distributed values and medians with first and third quartile for non-normally distributed values

* Liver fibrosis is defined as either cirrhosis or severe, portal-portal bridging fibrosis

** Considerable alcohol intake is defined as consumption of more than 1 standard drink (=10g ethanol) per day for women and more than 2 standard drinks for men

Because both cirrhosis and HCC are very rare with ferritin levels below 1000 µg/l (9,13,38-41), we compared patients with higher ferritin levels with and without HCC (Table 3) to evaluate for possible indicators for HCC in those patients most at risk. In comparing these two groups with univariate analysis, age at diagnosis still showed a significant difference. The other variables showing a significant association were serum ferritin, positive liver histology and BMI. Because higher BMI with increasing age could be a possible explanation for this association, we searched for a significant positive correlation between BMI and age, but no such correlation could be found.

Table 3. Comparison between Patients with HCC and Patients without HCC and Serum Ferritin >1000µg/l at the Time of Diagnosis of HH

	HCC (n=10)	Ferritin ≥1000µg/ml, no HCC (n=59)	p-values
Age at diagnosis, years (range)	61±11 (40-80)	48±10 (24-69)	<0.001
Male sex, % (n)	100% (10)	80% (47/59)	0.191
Body mass index, kg/m²	27±3	25±3	0.013
Serum ferritin, µg/l (Q1, Q3)	3704 (2025, 4463)	2115 (1493, 2830)	0.025
MCP-arthropathy, % (n)	80% (8/10)	54% (32/59)	0.174
Elevated transaminases, % (n)	100% (10/10)	68% (39/57)	0.052
Liver fibrosis on biopsy*, % (n)	90% (9/10)	50% (16/32)	0.031
Diabetes mellitus, %, (n)	10% (1/10)	8% (5/59)	1.000
Hypogonadism, % (n)	20% (2/10)	5% (3/59)	0.150
Considerable alcohol intake**, % (n)	20% (2/10)	23% (13/57)	1.000
Year of diagnosis (Q1, Q3)	2001 (1990, 2003)	1998 (1994, 2006)	0.552

Values are means±1 SD for normally distributed values and medians with first and third quartile for non-normally distributed values

* Liver fibrosis is defined as either cirrhosis or severe, portal-portal bridging fibrosis

** Considerable alcohol intake is defined as consumption of more than 1 standard drink (=10g ethanol) per day for women and more than 2 standard drinks for men

We performed a multiple logistic regression analysis to assess for the independent effect of the most relevant variables as shown in Table 4. The variables chosen for this analysis include those shown to be significant in the previous analysis (Table 3) as well as those found positive in all HCC patients (male sex, MCP arthropathy, elevated liver enzymes). We further included regular alcohol consumption, as it is an unrelated important etiology of cirrhosis and HCC (42). Liver histology was not included in this analysis because of the small number of patients who underwent liver biopsy. As all patients with HCC were male and had elevated liver enzymes and MCP arthropathy, Firth's penalized maximum likelihood estimation (35) was used to deal with the problem of quasi-complete separation. The only variable still significant in this analysis was age at diagnosis.

Table 4. Multiple Logistic Regression Comparing Patients with and without HCC

			95% CI for B			
	B	**standard error**	**lower**	**upper**	**Exp (B)**	**p**
Age at diagnosis	0.174	0.069	0.056	0.397	1.190	0.001
Male sex	0.365	1.661	-2.874	5.457	1.440	0.832
Serum ferritin	0.000	0.000	-0.001	0.001	1.000	0.790
Elevated liver enzymes	2.683	1.716	-0.193	7.974	14.636	0.071
Considerable alcohol intake*	0.125	1.227	-2.517	2.524	1.133	0.917
MCP-arthropathy	0.075	1.038	-2.095	2.330	1.078	0.944
Body mass index	0.196	0.166	-0.116	0.580	1.217	0.227

* Considerable alcohol intake is defined as consumption of more than 1 standard drink (=10g ethanol) per day for women and more than 2 standard drinks for men

To corroborate the finding of age as an independent risk factor, we executed the same analysis including the results of the liver biopsy (results not shown in table). When analyzing all patients with a serum ferritin level above 1000 µg/l who underwent liver biopsy at diagnosis of HH, age at diagnosis was still significantly higher among HCC patients (Exp(B) 1.213, p = 0.007; total of 40 cases analyzed). The other variables did not differ significantly. We further compared HCC patients with patients without HCC and very high ferritin levels (>2000 µg/l), which corresponds to a matched population for this variable. Age at diagnosis still proofed to be significantly higher among HCC patients (60.5±11 years vs. 48.4±7.8 years; p = 0.001; results not shown in table). Likewise, when including only patients with positive liver histology, HCC patients were significantly older than non-HCC patients (63.5±16 years vs. 50.0±7 years; p = 0.004; results not shown in table).

6 Discussion

6.1 Study Cohort

Our study was conducted in a large, clinically well defined cohort of HH patients followed up over a substantial period of time. The particularity of our cohort is that all patients had elevated iron parameters at diagnosis of HH, thus representing patients with phenotypic expression of the HFE-gene mutation. With patients recruited from a tertiary center as well as from primary care, we consider the cohort to adequately reflect the clinical picture of HH encountered in daily practice. We therefore argue that our findings are representative of hemochromatosis patients in Switzerland.

6.2 Clinical Presentation of Hereditary Hemochromatosis

In accordance with current literature(7,8,43), the presentation of HH at the time of diagnosis has shifted to a milder clinical picture. In our cohort, 29% of patients presented without signs or symptoms of secondary organ damage. In these patients, the only evidence of disease was an elevated serum ferritin level and/or an elevated transferrin saturation.

The most frequent abnormalities were elevated liver enzymes and arthropathy, particularly arthropathy of the MCP-joints II to V. Arthropathy of the MCP-joints II to V is a relatively specific and early sign for HH (44). Its presence should always prompt further investigation. Likewise, in the work-up of consistently elevated transaminases, HH is an important differential diagnosis to be considered. 24% of patients suffered from liver cirrhosis or severe fibrosis confirmed by biopsy. This might be an underestimation, as only 70 of 147 patients in the cohort underwent liver biopsy. We consider this an important number, as the presence of cirrhosis at diagnosis signifies a reduced life expectancy mostly through death by liver failure or HCC (9,11,25,37).

Hence we would like to raise the awareness of the milder clinical manifestations of HH to allow for timely diagnosis and treatment.

6.3 Hepatocellular Carcinoma: Prevalence and Risk Factors

The 9% overall prevalence of HCC as well as the prevalence of 33% among patients with cirrhosis is comparable to the values found in earlier studies (5,9,12,25,29,30,37). Contrary to the severity of the clinical picture, the prevalence of HCC among HH patients has not changed significantly over the last 40 years (5,28). This is also supported by the fact that the year of diagnosis did not differ significantly between patients with and without HCC in our cohort.

With the overwhelming majority of HCC cases developing in cirrhotic livers (5,25,30,41,45), cirrhosis is a well-known risk factor for HCC. Because the development of liver cirrhosis and other secondary organ damage correlates with the severity of iron overload (37,46), it is plausible that HCC patients have significantly higher ferritin levels at diagnosis.

In addition to these two established risk factors for HCC, we showed that age at diagnosis of HH is also linked to an increased risk. In our cohort, age at diagnosis was independently associated with HCC, especially among patients with high iron overload (serum ferritin

>1000 µg/l at diagnosis) and even among those with cirrhosis. With an increase in odds by a factor of 5.7 for a 10 year-increase in age, age at diagnosis considerably adds to the risk for HCC (Table 4). As progressive accumulation of iron with increasing age is assumed in patients without therapeutic phlebotomy or other forms of blood loss (5,47), we consider age at diagnosis to be a surrogate marker for the duration of exposure to iron overload. Hence it seems that not only the amount of iron, but also the duration of exposure to toxic levels of iron is important for the degree of damage done to the liver. The lack of significance of serum ferritin in the multiple logistic regression analysis suggests that above a certain threshold of iron overload (i.e. serum ferritin >1000 µg/l), the duration of exposure may be more important for the development of HCC than the exact amount of the liver iron burden itself.

There are several pathological and experimental studies providing evidence for the direct carcinogenic effects of iron through oxidative stress and epigenetic DNA modification (13,41,48,49) without the "inflammation - cirrhosis - carcinoma" sequence. This could be a possible explanation for our finding. It was shown that HH patients with longstanding iron overload have specific epigenetic defects in non-neoplastic hepatocytes which are typical of HCC (49). This effect was independent of the presence of cirrhosis (49). Another indication is the histological description of iron free foci in both cirrhotic and non-cirrhotic livers of HH patients and their role as preneoplastic lesions (13,41,48,50,51). Interestingly, one patient in our cohort who later developed HCC had a normal liver biopsy at diagnosis of HH and no further risk factors for HCC. This case as well as numerous other case reports of patients with HH who developed HCC in non-cirrhotic livers (41,51-58) underline the possible development of HCC independent of cirrhosis.

A possible limitation of our study is the fact that not all patients underwent liver biopsy at the time of diagnosis of HH. This led to a smaller sub-group analysis with multiple logistic regression when including the histological results. Therefore, no final conclusion can be drawn about the magnitude of the influence of cirrhotic remodeling on the development of HCC. As liver biopsy is no longer needed for the diagnosis of HH (43), this will likely remain a problem for future studies.

No conclusion can be made from our study about the influence of concurrent chronic viral hepatitis, as only three patients (all without HCC) suffered from chronic hepatitis B or C. Contrary to other studies (41,45), we could not find a significant association between regular alcohol consumption and development of HCC. A possible explanation could be the low prevalence of heavy alcohol abuse in our cohort (only five patients who consume more than 300 g of ethanol per week). The association of BMI with HCC might be explained by the higher prevalence of non-alcoholic fatty liver disease (NAFLD) with increasing BMI, which can also lead to HCC (59). We cannot make a statement in this regard from our study due to the lack of information about NAFLD in biopsy specimens.

HCC discovered at a symptomatic stage generally has a poor prognosis, because curative surgical or interventional options are usually no longer available (60). Therefore, screening of high risk populations is recommended to detect HCC at an early stage (43,61). According to current guidelines, screening of HH patients is only recommend in the presence of cirrhosis (43). It should be continued throughout life (or as long as a curative surgical intervention is feasible and reasonable), as HCC can develop many years after the achievement of iron depletion (25,37).

The challenge remains to adequately select non-cirrhotic patients for screening. Wise selection of patients for screening could aid in the early diagnosis of HCC in the rare cases where it develops in non-cirrhotic livers. Our finding of age at diagnosis of HH as an independent risk factor can help in making the decision for appropriate screening measures for the individual patient.

6.4 Conclusions

It is important for the clinician to be aware of the frequency of HH and its milder clinical picture in our era to allow for early diagnosis and treatment. MCP arthropathy and elevated liver enzymes are the most common manifestations and should always lead to further investigations when present.

With an overall prevalence of 9%, HH still carries a substantial risk of HCC. Patients with a high risk of HCC should be regularly screened to allow for early diagnosis and possible curative treatment of HCC. Our finding of age at diagnosis of HH as an independent risk factor for HCC, especially among patients with high iron overload, should be taken into consideration when deciding on an individual patient's need for screening for HCC.

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